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(54) Title: AEROSOL DRUG FORMULATIONS CONTAINING VITAMIN E

(57) Abstract

Pharmaceutical compositions for aerosol delivery comprising (a) a medicament, (b) a non-chlorofluorocarbon propellant, and (c) tocopherol or a pharmaceutically acceptable derivative thereof, as well as a method for preparing such compositions in which unwanted aggregation of the medicament is prevented without the use of surfactants or cosolvents.

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AEROSOL DRUG FORMULATIONS CONTAINING VITAMIN E

The present invention relates to drug formulations for aerosol delivery which are compatible with non-chlorofluorocarbon propellants, and especially to excipients which are useful therein. In particular, the invention relates to inhalable formulations comprising tocopherol (vitamin E) or tocopherol analogs or derivatives, which formulations possess a variety of advantageous properties.

BACKGROUND OF THE INVENTION

Numerous pharmaceutical compounds are preferentially delivered by means of metered dose inhalation (MDI) devices, in which a physiologically inert propellant of high vapor pressure is used to discharge a precise amount of medication with each operation. These MDI devices, also known as aerosols or inhalers, have found widespread use among patients suffering, for example, from episodic or chronic asthma. The propellants of choice have historically been chlorofluoro-carbons, such Propellant 11 (trichlorofluoromethane), Propellant 12 (dichlorodifluoromethane) and Propellant 114 (dichlorotetrafluoroethane).

In recent years, however, there have been growing concerns that chlorofluorocarbon (CFC) propellants have detrimental environmental effects, and in particular that they interfere with the protective upper-atmosphere ozone layer. Under an international accord (the Montreal Protocol), the use of CFC propellants will be prohibited by the start of the year 2000, and possibly sooner. Alternative propellant vehicles are being developed which exhibit little or no ozone depletion potential (ODP). Such alternative propellants include two -- HFC-134a (1,1,1,2-tetrafluoroethane) and HFC-227ea (1,1,1,2,3,3,3-heptafluoropropane) -- which have negligible ODP and are currently undergoing safety and environmental testing.

Unfortunately, surfactants which are generally used in known MDI formulations have been found to be imiscible in and therefore incompatible with these new, non-CFC propellants. Such surfactants are necessary to prevent aggregation (in the form of "caking" or crystallization, for example) of the medicinally active compound in the reservoir of the inhaler, to facilitate uniform dosing upon aerosol administration, and to provide an aerosol spray discharge having a favorable respirable fraction (that is, a particle size distribution such that a large portion of the discharge reaches the alveoli where absorption takes place, and thus producing high lung deposition efficiencies). To overcome this incompatibility, it has previously been taught to include cosolvents (such as ethanol) with the non-CFC propellants so as to blend the surfactants into the formulation. Another suggested approach has been to emulsify the MDI formulation in the presence of a surfactant with low-vapor pressure additives, such as polyhydroxy alcohols as for example propylene glycol.

Such cosolvents or additives may of course be physiologically active, and in some instances may not be tolerated by the user of an MDI medication. There is therefore a need for MDI formulations compatible with non-CFC, non-ozone depleting propellants, which prevent aggregation of drug particles without the use of cosolvents or similar carrier additives, and which provide uniformity of dosing and a favorable respirable fraction.

SUMMARY OF THE INVENTION

It has now been found that tocopherol, or vitamin E, and its derivatives are capable of stabilizing MDI formulations utilizing the propellants HFC-134a and HFC-227ea so as to (i) prevent aggregation, (ii) provide dosing uniformity, and (iii) afford high lung deposition efficiency without the need for either surfactants or cosolvents. Additionally, the tocopherol has the unexpected benefit of providing adequate lubrication for the valve used in an MDI product without the need for additional lubricants, thus aiding satisfactory functioning of the aerosol device throughout the life of the product.

The tocopherols utilized herein are known to be biocompatible (or even beneficial), and present no known toxicologic or pathologic consequences at the concentrations proposed for their use. Non-CFC formulations which include tocopherols do not require the addition of cosolvents or even of conventional surfactants such as sorbitan trioleate (SPAN 85), sorbitan monooleate and oleic acid, yet provide high lung deposition efficiencies and respirable fractions comparable to those obtained with known CFC-propellant formulations. It is thus expected that non-CFC formulations comprising tocopherols will be useful for the delivery of both peptide and non-peptide pharmaceutical medicaments for which MDI delivery is deemed favorable.

Accordingly, in one aspect of the present invention are disclosed pharmaceutical compositions for aerosol delivery, as for example by inhalation and pulmonary absorption, comprising a therapeutically effective amount of a medicament, a non-chlorofluorocarbon propellant, and tocopherol. The propellant in such compositions are preferably fluorocarbons and, more preferably, the non-ozone depleting fluorocarbons HFC-134a or HFC-227ea. The medicament in the compositions of the invention are preferably LHRH analogs, 5-lipoxygenase inhibitors, immunosuppressants or bronchodilators; especially preferred medicaments include leuprolide acetate, the LHRH antagonist Ac-D-2-Nal-D-4-ClPhe-D-3-Pal-Ser-N-MeTyr-D-Lys(Nic)-Leu-Lys(N-Isp)-Pro-D-Ala-NH_2 (hereinafter "D-2-Nal"), the 5-lipoxygenase inhibitor N-[3-[5-(4-fluorophenylmethyl)-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea, the immunosuppressant cyclosporine, and the adrenergic bronchodilator isoproterenol. (As used herein, "5-lipoxygenase inhibitor", or "5-LO inhibitor", refers to any physiologically active compound capable of affecting leukotriene biosynthesis.)

The tocopherol used in the pharmaceutical compositions of the present invention may be vitamin E or any of its pharmaceutically acceptable derivatives which are well tolerated upon inhalation. Suitable forms of tocopherol may include, but are not limited to, *d*- or *dl*-alpha tocopherol ($C_{29}H_{50}O_2$), *d*- or *dl*-alpha tocopheryl acetate ($C_{31}H_{52}O_3$), and *d*- or *dl*-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$), as well as mixtures thereof.

The tocopherol of the present invention may be present in a concentration of between about 0.00001% and about 10% by weight, and preferably in a concentration of between about 0.001% and about 5% by weight.

In a further aspect of the present invention is disclosed a method of preparing a stable suspension of particles of a medicament in a liquid phase non-chlorofluorocarbon aerosol propellant, which method comprises the addition to the suspension of tocopherol in an amount sufficient to prevent aggregation of the particles. Preferably, the tocopherol may be added in an amount of between about 0.00001% and about 10% by weight; more preferably, the tocopherol may be added in an amount of between about 0.001% and about 5% by weight. The propellants, medicaments and tocopherols suitable for use in the method of the present invention are those described above in connection with the pharmaceutical compositions of this invention.

DETAILED DESCRIPTION OF THE INVENTION

It is expected that numerous non-ozone depleting aerosol propellants may be used with the compositions and methods of the present invention. These include not only HFC-134a and HFC-27ea, described above, but also halogenated alkanes in general, such as HCFC-123 (1,1,1-trifluoro-2,2-dichloroethane), HCFC-124 (1,1,1,2-tetrafluorochloroethane), HCFC-141b, HCFC-225, HFC-125, FC-C51-12 (perfluorodimethylcyclobutane), DYMEL A (dimethyl ether) and DYMEL 152a (1,1-difluoroethane).

It is further expected that the compositions and methods of the invention will be suitable for the administration of a wide variety of peptide and non-peptide drugs. Examples of peptides which may be delivered in this fashion are interferons and other macrophage activation factors, such as lymphokines, muramyl dipeptide (MDP), γ-interferon, and interferons a and b, and related antiviral and tumoricidal agents; opioid peptides and neuropeptides, such as enkaphalins, endorphins and dynorphins, and related analgesics; renin inhibitors including new-generation anti-hypertensive agents; cholecystokinins (CCK analogs) such as CCK, ceruletide and eledoisin, and related cardiovascular- and CNS-targeting agents; leukotrienes and prostaglandins, such as oxytocin, and related antiinflammatory, oxytocic and abortifacient compounds; erythropoietin and analogs thereof, as well as related haematinics; LHRH analogs, such as leuprolide, buserelin and nafarelin, and related down-regulators of pituitary receptors; parathyroid hormone and other growth hormone analogs; enzymes, such as DNase, catalase

and alpha-1 antitrypsin; immunosuppressants such as cyclosporin; GM-CSF and other immunomodulators; and insulin. Such peptides or peptide analogs are frequently not well-absorbed when given orally.

Examples of non-peptides which may readily be delivered using the compositions and methods of the present invention are beta-agonists, such as isoproterenol, albuterol, isoetherine and metoproteronol, and related anti-asthmatics; steroids, such as flunisolide, and similar anti-asthmatics; cholinergic agents, such as cromolyn, and related anti-asthmatics; and 5-lipoxygenase inhibitors, such as zileuton and the hydroxyurea compound described above, and related leukotriene inhibitors. Such non-peptides may lend themselves to oral administration, but when given by inhalation are found to produce rapid reversal of bronchoconstriction in cases of allergic airway disease and asthma. Also, these compounds may be administered more frequently as MDI formulations than when given orally.

It is also expected that analogs and derivatives of the above tocopherols will be identified which are suitable for use in the compositions and methods of the present invention. To the extent that these analogs and derivatives are similar in structure to or are readily obtained by chemical modification of the tocopherol molecule, while substantially retaining the physical properties and biocompatibility of vitamin E, such analogs and derivatives are intended to be included among the compositions and methods of the present invention.

The medicaments useful in the compositions of the present invention include not only those specifically named above, but also where appropriate the pharmaceutically acceptable salts, esters, amides and prodrugs thereof. By "pharmaceutically acceptable salts, esters, amides and prodrugs" is meant those carboxylate salts, amino acid addition salts, esters, amides and prodrugs of a compound which are, within the scope of sound medical judgement, suitable for use in contact with with the tissues of humans and lower animals with undue toxicity, irritation, allergic response and the like, commensurate with a reasonable benefit/risk ratio and effective for their intended use.

The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of a medicinal compound. These salts can be prepared *in situ* during the final isolation and purification of the compound or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate and laurylsulphonate salts and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium,

calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. (See, for example S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66:1-19 (1977).)

Examples of pharmaceutically acceptable, non-toxic esters of a compound include (C_1-to-C_6 alkyl) esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include (C_5-to-C_7 cycloalkyl) esters as well as arylalkyl esters such as, but not limited to, benzyl; (C_1-to-C_4 alkyl) esters are preferred..

Examples of pharmaceutically acceptable, non-toxic amides of medicinal compounds include amides derived from ammonia, primary (C_1-to-C_6 alkyl) amines and secondary (C_1-to-C_6 dialkyl) amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, (C_1-to-C_3 alkyl) primary amides and (C_1-to-C_2 dialkyl) secondary amides are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent medicinal compound, as for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press (1987).

When used in the above compositions, a therapeutically effective amount of a medicament of the present invention may be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester or prodrug form. By a "therapeutically effective amount" of a medicament is meant a sufficient amount of the compound to obtain the intended therapeutic benefit, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the medicaments and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the

art to start doses at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The total daily doses of the medicaments contemplated for use with this invention, and consequently the concentrations by weight of the medicaments in the respective compositions, may vary widely. In the case of an LHRH analog, such as leuprolide acetate, the intended daily dose may range from about 0.01 to about 5 mg/day; accordingly, where an aerosol inhaler is to be used several times a day with a discharge volume of between about 5 and about 250 µl, the concentration of medicament will be between about 0.2 and about 20 mg/ml. Similarly, in the case of a 5-lipoxygenase inhibitor expected to be administered in a daily dose ranging from about 0.01 to about 10 mg/kg/day, the concentration will be between about 0.001 and about 100 mg/ml. Of course, medicament concentrations outside of these ranges may also be suitable, where different potencies, dosing frequencies and discharge volumes are used.

The compositions of the invention may be prepared by combining tocopherol with a medicament which has been milled or otherwise reduced to a desired particle size, and placing the mixture in a suitable aerosol container or vial. After sealing the container, an aerosol propellant is introduced and the system is agitated to fully blend the ingredients. Alternatively, the tocopherol and medicament may be milled together, either before or after addition of propellant. In some instances, it may be necessary to wet-mill the medicament in a closed system, as for example under temperature and pressure conditions which permit the medicament to be milled while mixed with a liquid-phase aerosol propellant. It is expected that, for any particular combination of medicament, propellant and tocopherol, the ideal order of addition of ingredients and the conditions under which they are to be combined may readily be determined.

The compositions and methods of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention. Both below and throughout the specification, it is intended that citations to the available literature are expressly incorporated by reference.

Example 1

Physical Stability of MDI Formulations Containing Tocopherol

A determination of the effect of tocopherol on the physical stability of several MDI formulations prepared with HFA-134a was conducted as follows: *d*-Alpha tocopheryl acetate USP (Aldrich Chemical Co. Inc., Milwaukee, Wisconsin) and each of the drugs being formulated were combined in the amounts shown in appropriate transparent aerosol containers (vials). (Leuprolide acetate and its preparation are described in United States Patent No. 4,005,063, issued January 25, 1977; the LHRH antagonist D-2-Nal and its preparation are described in United States Patent No. 5,110,904, issued May 5, 1992; and the 5-LO inhibitor N-[3-[5-(4-fluorophenylmethyl)-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea and its preparation are described in United States Patent No. 5,288,751, issued February 22, 1994; each of which disclosures are incorporated herein by reference.) Additionally, to some of the vials was added a dispersant/stabilizer, sodium decanesulfonate ("DSA", Aldrich Chemical Company, Inc.), in an amount to produce a final concentration of 0.1% by weight. The vials were crimped and charged with approximately 10 mL of HFC-134a and agitated to blend the ingredients. The dispersion quality in each preparation was evaluated visually after 24 and 48 hours.

Results of these tests are shown below in Table 1. The data obtained show that tocopherol produces good dispersion quality, even in the absence of DSA. By comparison, control formulations of each of the test compounds (which were prepared without tocopherol or DSA) were seen to have poor dispersion quality after less than 30 seconds.

Table 1

Dispersion Quality of Selected Drugs in HFA-134a

Active Ingredient	Tocopheryl Ac Concentration	DSA Concentration	Dispersion Quality 24 Hours	48 Hours
Leuprolide Acetate	0.1%	0	Good	Good
"	0.2%	0	Good	Good
"	0.3%	0	Good	Good
"	0.1%	0.1%	Good	Good
"	0.2%	0.1%	Good	Good

LHRH Antagonist	0.1%	0	Good	Good
"	0.2%	0	Good	Good
"	0.3%	0	Good	Good
"	0.1%	0.1%	Good	Good
5-LO Inhibitor	0.1%	0	Good	Good
"	0.2%	0	Good	Good
"	0.3%	0	Good	Good
"	0.1%	0.1%	Good	Good
"	0.2%	0.1%	Good	Good
"	0.3%	0.1%	Good	Good

Example 2

Preparation of MDI Formulations for Performance Testing

For each test formulation, between 7 and 12 g of glass beads were placed into a suitable glass aerosol container (vial), along with 100 mg to 250 mg drug and tocopheryl acetate in the amounts needed to produce the desired final concentrations. The vials were crimped shut with valves having delivery values (volumes per spray) of either 50 µl or 100 µl, and then charged with 10 ml of HFA-134a propellant. The filled vials were then shaken for 24 hours to mill and disperse the drug, after which testing was carried out *in vitro* or *in vivo* as described below.

Example 3

Uniformity of MDI Delivery of Compositions Containing Tocopherol

Delivery uniformity and physical stability of the compositions of the invention containing the 5-LO inhibitor were tested as follows: Each vial was shaken and its valve primed by aerosolizing 5 times in succession, after which the vial was weighed. The vial was then actuated a fixed number of times (5 times per cycle), followed by another weighing. This process was repeated until shot weights began to drop off appreciably ("tail-off").

The amounts delivered were calculated as total weight per cycle (5 sprays) and compared to a target value, in each case, of 305 mg. Also calculated were the number of cycle weight measurements which fell within upper and lower range limits of 110% and 90% of the target weight, respectively.

The results of these studies, shown below in Table 2, demonstrate the uniformity with which the compositions of the present invention are delivered by a MDI device. In each instance, the success rate is the number of 5-shot cycles falling between the upper and lower range limits, relative to the total number of cycles measured, prior to tail-off.

Table 2

Delivery of 5-LO Inhibitor Compositions Containing Tocopherol

Drug Concentration	Tocopheryl Ac Conc.	Success Rate
1.0%	0.1%	32/33 (97%)
1.0%	0.1%	34/34 (100%)
1.0%	0.2%	33/33 (100%)
2.0%	0.1%	33/34 (97%)
2.5%	0.2%	35/36 (97%)
2.5%	0.3%	32/32 (100%)

Example 4

Uniformity of MDI Delivery of Compositions Containing Tocopherol

The experiments of Example 3 were repeated using cyclosporin (cyclosporine A) and isoproterenol base (Sigma Chemical Co., St. Louis, Missouri). In the case of cyclosporin, a formulation of the invention containing 2.5% drug and 0.1% tocopheryl acetate in HFC-134a propellant was prepared as before, primed, and aerosolized into a beaker for six cycles of three sprays each. In the case of isoproterenol, each of two formulations containing 2.5% drug and 0.1% tocopherol in HFC-134a propellant was prepared as before, primed, and aerosolized into a beaker for a single cycle of five sprays. In both cases, shot weights were recorded by measuring the weight of the aerosol vials before and after the cycle; additionally, unit spray contents (actual weights of drug sprayed per cycle) were determined by high performance liquid chromatography analysis of appropriate solvents (such as ethanol) placed in each of the beakers before testing.

For both drugs and for all testing cycles, shot weights and unit spray contents were well within the upper and lower range limits of 110% and 90% of the target values, demonstrating the applicability of the compositions of the present invention to a variety of pharmaceutical agents.

Example 5

Bioavailability of MDI Compositions Containing Tocopherol

Using a test preparation of the 5-LO inhibitor containing 1.275% (by weight) drug and 0.05% (by weight) tocopheryl acetate in HFC-134a propellant, bioavailability of aerosol-delivered drug was compared to that of an aqueous control formulation delivered intravenously (IV). Eight tracheostomized beagle dogs (two-year-old females, Marshall Labs) were used for each group. To the dogs in the IV group, 0.5 mg/kg drug was given intravenously over a 1 minute period as a 1 mg/ml solution in 60% PEG 400 (polyethylene glycol, Union Carbide Co., Institute, W. Virginia) in water. To the dogs in the aerosol group, the same amount of drug was administered by sprays of the test formulation delivered into the trachea. Blood samples were collected at specified time intervals and analyzed for drug concentration using high performance liquid chromatography.

The results of these studies, shown below in Table 3, demonstrate that drugs are effectively administered using the MDI formulations of the present invention. In particular, bioavailability of the aerosolized drug over a 24-hour period was 42% that of the same amount delivered intravenously, based on area-under-curve (AUC) calculations. Net bioavailability was even better: When corrected for non-absorptive loss of drug (as for example due to loss in the dosing device, inertial impaction of the spray in the trachea, and expulsion with exhaled air), bioavailability exceeded 80% of that obtained using intravenous administration.

Table 3

Comparison of Intravenous and MDI Delivery of 5-LO Inhibitor

	Intravenous	Aerosol
C_{max} (μg/ml)	0.73 ± 0.07	0.19 ± 0.08
T_{max} (hours)	---	10.67 ± 7.06
AUC_{0-24} (μg•hour/ml)	5.89 ± 0.73	2.53 ± 1.03

Similar studies were carried out using MDI formulations of the invention containing leuprolide acetate in place of the 5-LO inhibitor. The results obtained were virtually identical to those above, in that bioavailability was found to be approximately 42% and more than 80% (with and without correction for non-absorptive loss, respectively) of that achieved using intravenous administration.

It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the substituents, means of preparation and/or methods of use of the invention, may be made without departing from the spirit and scope thereof.

What is claimed is:

1. A pharmaceutical composition for aerosol delivery comprising a medicament, a non-chlorofluorocarbon propellant, and tocopherol.

2. A pharmaceutical composition according to Claim 1 wherein the propellant is a halogenated alkane.

3. A pharmaceutical composition according to Claim 2 wherein the propellant is selected from the group consisting of HFC-134a and HFC-227ea.

4. A pharmaceutical composition according to Claim 2 wherein the tocopherol is present in a form selected from the group consisting of *d*-alpha tocopherol, *dl*-alpha tocopherol, *d*-alpha tocopherol acetate, *dl*-alpha tocopherol acetate, *d*-alpha tocopherol acid succinate and *dl*-alpha tocopherol acid succinate.

5. A pharmaceutical composition according to Claim 1 wherein the tocopherol is present in a concentration of between 0.00001% and 10% by weight.

6. A pharmaceutical composition according to Claim 1 wherein the tocopherol is present in a concentration of between 0.001% and 5% by weight.

7. A pharmaceutical composition according to Claim 3 wherein the medicament is selected from the group consisting of LHRH analogs, 5-lipoxygenase inhibitors, immunosuppressants and bronchodilators.

8. A pharmaceutical composition according to Claim 2 wherein the medicament is selected from the group consisting of leuprolide acetate, Ac-D-2-Nal-D-4-ClPhe-D-3-Pal-Ser-N-MeTyr-D-Lys(Nic)-Leu-Lys(N-Isp)-Pro-D-Ala-NH_2; N-[3-[5-(4-fluorophenylmethyl)-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea; cyclosporine; and isoproterenol.

9. A pharmaceutical composition according to Claim 8 wherein the propellant is HFC-134a.

10. A pharmaceutical composition according to Claim 9 wherein the tocopherol is present in a concentration of between 0.001% and 5% by weight.

11. A method of preparing a stable suspension of particles of a medicament in a liquid phase non-chlorofluorocarbon aerosol propellant, comprising the addition to the suspension of tocopherol in an amount sufficient to prevent aggregation of the particles.

12. A method according to Claim 11 wherein the propellant is selected from the group consisting of HFC-134a and HFC-227ea.

13. A method according to Claim 11 herein the tocopherol is in a form selected from the group consisting of *d*-alpha tocopherol, *dl*-alpha tocopherol, *d*-alpha tocopherol acetate, *dl*-alpha tocopherol acetate, *d*-alpha tocopherol acid succinate and *dl*-alpha tocopherol acid succinate.

14. A method according to Claims 12 or 13 wherein the medicament is selected from the group consisting of leuprolide acetate, Ac-D-2-Nal-D-4-ClPhe-D-3-Pal-Ser-N-MeTyr-D-Lys(Nic)-Leu-Lys(N-Isp)-Pro-D-Ala-NH_2; N-[3-[5-(4-fluorophenylmethyl)-2-thienyl]-1-methyl-2-propynyl]-N-hydroxyurea; cyclosporine; and isoproterenol.

INTERNATIONAL SEARCH REPORT

Interna[illegible]l Application No PCT/US 95/02764

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 9/12,A 61 K 9/72,A 61 K 31/355

According to International Patent Classification (IPC) or to both national classification and IPC 6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A, 93/15 715 (IG SPRÜHTECHNIK GMBH) 19 August 1993 (19.08.93), claims 1,6-9.	1,4-7
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[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
02 May 1995	06.06.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	MAZZUCCO e.h.

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INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/US 95/02764

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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ANHANG

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

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ANNEXE

au rapport de recherche international relatif á la demande de brevet international n°

PCT/US 95/02764 SAE 106209

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés á titre indicatif et n'engagent pas la responsibilité de l'Office.

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